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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/672,763	09/26/2003	David J. Yang	UTSC:664USC1	1049

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EXAMINER	
JONES, DAMERON LEVEST	
ART UNIT	**PAPER NUMBER**
1618	

DATE MAILED: 10/11/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/672,763	YANG ET AL.	
	Examiner	Art Unit	
	D. L. Jones	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 July 2006 and 25 September 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *52-82* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *52-70, 73, 79, and 80* is/are rejected.

7)☒ Claim(s) *71,72,74-78,81 and 82* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/25/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

ACKNOWLEDGMENTS

1. The Examiner acknowledges receipt of the amendment filed 7/19/06 wherein claims 1-51 are canceled. In addition, the Examiner acknowledges receipt of the declaration filed 7/19/06 under 37 CFR 1.131.

Note: Claims 52-82 are pending.

RESPONSE TO APPLICANT'S ARGUMENTS/AMENDMENT

2. The Applicant's arguments and/or amendment filed 7/19/06 to the rejection of the claims made by the Examiner under 35 USC 103 have been fully considered and deemed because Applicant has submitted a persuasive declaration to overcome the art rejection.

COMMENTS/NOTES

3. In Applicant's response filed 7/19/06, it is stated that Anderson et al alone fails to obviate the instant invention. In particular, Applicant discloses that Anderson et al makes reference to the observation that an indium complex with excellent in vivo stability is desirable when designing bifunctional chelates conjugated to larger molecules such as antibodies or peptides. Applicant's position is that the reference does not identify any BAT conjugates per se and that the article itself suggests that it would be unpredictable whether a chelate conjugated to a protein or peptide would be stable in vivo. Hence, Applicant has concluded that the Anderson et al reference is simply nothing more than an 'obvious to try' reference.

103 REJECTIONS

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 52-70, 73, 79, and 80 are rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson et al (Nucl. Med. Biol., 1995, Vol. 22, No. 2, pp. 165-173) in view of Sun et al (J. Med. Chem., 1996, Vol. 39, pp. 458-470) in further view of McBride et al (US Patent No. 5,620,675), Nosco et al (US 4,925,650), and Linder et al (US Patent No. 5,688,487).

Anderson et al disclose N,N'-ethylene-di-L-cysteine (EC) complexes of Ga (III) and In(III). The chelates contain two nitrogens and two sulfurs (N2S2). N,N'-ethylene-di-L-cysteine is a N2S2 ligand that also contains two carboxylic acid moieties for complexation of Ga(III) and In(III). Also, Anderson et al discloses that because of the high thermodynamic and in vivo stability of In-EC, derivatives of EC may have applications as bifunctional chelates for 111In labeled proteins and peptides. The 68Ga-EC complex are possible myocardial PET imaging agents. The radiolabeled complex was injected into rat and various tissues and organs (e.g., lung, liver, and brain) were observed (see entire document, especially, abstract; page 167-168, bridging paragraph; page 171, Table 5; page 172, Table 6). However, Anderson et al fail to specifically disclose a method of imaging wherein 68Ga and various other radionuclides are utilized even though the reference discloses that that lipophilic analogues of 68Ga-

EC have potential as myocardial PET imaging agents. In addition, Anderson et al fail to disclose a targeting agent (i.e., protein or peptide) attached to EC. Furthermore, Anderson et al fail to disclose various other possible dicarboxylic acid containing BAT derivatives that may be used in their invention.

Sun et al disclose indium and gallium complexes of bis(aminoethanethiol) ligands (see entire document, especially, abstract). In addition, Sun et al that over the past 15 years various kinds of bis(aminoethanethiol) [BAT or dithiadiaza (N2S2)] ligands have been evaluated as radiopharmaceuticals. Sun et al refers to Anderson et al (the primary reference cited above). Sun et al discloses that Anderson et al reported the in vivo stability of N,N'-ethylene-di-cysteine (EC) with gallium and indium (page 459, column 1, second complete paragraph). Also, Sun et al disclose that it is known in the art that N,N'-bis(2-mercaptoethyl)-ethylenedieamine-N,N'-diacetic acid (EDDASS) has an usually high affinity for indium and that the ligand has two mercaptoethyl groups replacing two carboxylates of EDTA. The potential of dithiadiaza-containing ligand for use in nuclear medicine, especially for the application of chelates as imaging agents. Thus, a series of multidentate ligands, including N,N'-bis(2,2-dimethyl-2-mercaptoethyl)ethylenediamine-N,N'-diacetic acid (6SS, see page 459 for structures of EDDASS and 6SS) which contains two amino donors and two mercaptoethyl donors. In the structures disclosed by Sun et al the number of carboxyl groups attached to the structures varies. Each ligand was synthesized and the *stabilities* of their indium and gallium complexes were determined (page 459, columns 1-2, bridging paragraph; page 461, second column, 'Serum Stability Studies'; page 468, 'Stability Constants and

'Effects of gem-Dimethyl Groups in Ligand Design'). Male rats with injected with the various ligand compositions (pages 461-462, bridging paragraph). Furthermore, Sun et al disclose that the liver clearance of the Ga and In complexes indicated that the more stable complexes are cleared rapidly whereas the less stable complexes were retained in the liver. Finally, Sun et al concluded that chelating agents that form the most stable complexes of gallium or indium and which are cleared from the liver the most rapidly would be the best candidates for forming bifunctional ligands which can be covalently linked to biomolecules. Hence, the bifunctional chelating agents offering the best chances of success would be derived from 6SS and EDDASS (page 469, column 1, fourth complete paragraph).

McBride et al disclose radioactive peptides (see entire document, especially, abstract). The imaging agents of McBride et al comprise a targeting moiety (i.e., peptide) and a radiolabel binding moiety which is *stably* complexed with various radioisotopes (column 6, lines 20-28; column 10, lines 44-51). The peptide may be linked to a bisamino bisthiol radiolabel binding moiety (column 8, lines 13-33 and 46-48). The imaging agents of McBride et al may be used for various applications such as diseases and ailments (i.e., diabetes, cirrhosis, hepatitis *infection*, bleeding ulcers, gastrointestinal bleeding, pancreatitis, central nervous system disorders, endocrine disorders, Alzheimer's disease, acromegally, and cancer (column 10, lines 18-29). Also, McBride et al disclose a BAT derivative that contains a single carboxylic group (column 12, lines 29-30, a structural depiction of the BAT derivative is included with this office action.

Nosco et al disclose complexes useful for examining renal function (see entire document, especially, abstract). In particular, Nosco et al disclose that the complexes may have multiple carboxylic acid groups (abstract). The complexes which are labeled with technetium-99m are suitable for examining renal function have high organ specificity and improved stability (see column 2, lines 63-68). For Formula I, when Z is sulfur and either one of the provisos that (a) if R15, R16, R17, and/or R18 are/is ACOOH; (b) at least one of the symbols R1-R18 is ACOOH; or (c) if t = 1, at least two of the symbols R1-R18 are ACOOH, multiple carboxylic acid groups may be present on the BAT derivative (column 3, lines 5-41). Nosco et al disclose two BAT derivatives, N,N'-bis(1-carboxy-2-mercaptoethyl)ethylene diamine and N,N'-[bis(2-mercaptoethyl)]-N,N'-ethylenediamino-diacetic acid, having two carboxylic acid groups (column 4, lines 39 and 43-44 and columns 8 (Example V) and 9 (Example VI), structural depictions of the compounds are included with this office action). The compositions are administered to living subjects and may be analyzed using a gamma camera (column 4, lines 51-60). Also, in column 5, lines 39-40, Nosco et al disclose that examples of suitable chelators for the radionuclide include dicarboxylic acids.

Linder et al disclose diagnostic imaging method using rhenium and technetium complexes which contain a hypoxia-localizing moiety (see entire documents, especially, abstract; column 6, lines 44-47). In addition, Linder et al disclose that the ligands that may be present in the complexes include N2S2 structures (diaminodithiol containing structures, column 3, Formula Ib). The complexes may be used for imaging of hypoxic

tissue and pathological conditions such as those found in the heart, brain, lungs, liver, kidneys, or in tumors (column 6, lines 53-57).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Anderson et al with those of Sun et al, McBride et al, and Nosco et al to generate a method as set forth in independent claim 52 for the following reasons. (1) Sun et al is cited to emphasis the teachings of Anderson et al in regards to the stability of the BAT derivatives and disclose possible BAT derivatives of interest as radiopharmaceuticals. Furthermore, Sun et al is cited to emphasis why a skilled practitioner in the art would be motivated to attach a targeting moiety to the ligand. Specifically, Sun et al disclose that the best candidates for forming bifunctional ligands which are covalently linked to *biomolecules* would be 6SS and EDDASS, both of which contain two carboxylic acid groups. (2) McBride et al is cited for its teachings that it is known in the art to generate imaging agents comprising a metal, targeting agent (i.e., peptide), and a BAT ligand. While the BAT derivatives of McBride contain a single carboxylic acid group, a skilled practitioner in the art would be motivated to replace the BAT derivatives of McBride with a more stable BAT derivative as disclosed by Sun et al. Thus, the attachment of a targeting agent to the chelators of Sun et al would be obvious to a skilled practitioner in the art. (3) Nosco et al disclose the it is known in the art that to utilize dicarboxylic acid containing ligands which are stable complexes for analyzing biological functions. (4) Linder et al is cited for its teachings of using a metal complex attached to a hypoxia localizing moiety in combination with a diaminodithiol containing moiety. Since each of the references are directed to BAT

derivatives that may be used for diagnostic and/or therapeutic purposes, the references may be considered to be within the same field of endeavor. Thus, the reference teachings are combinable. As a result, a skilled practitioner in the art would be motivated to interchange the BAT derivatives to the more stable complexes taught by Sun et al and Nosco et al for other BAT derivatives that are commonly used in the art in combination with a targeting agent and radionuclide. Furthermore, a skilled practitioner in the art would be motivated to attach various targeting agents to the complexes as disclosed in the cited prior art references since it is well known in the art, as indicated by the cited references above, to attach a targeting agent to deliver a composition to a particular site of interest. In addition, a skilled practitioner in the art would recognize that if one targets a tumor then a tumor marker is utilized. In the art the terms, antibody, protein, and peptide are often used interchangeably, thus, a tumor marker that is an antibody is within the skilled of a practitioner in the art. Also, a targeting agent that is an anticancer agent is within the skill of a practitioner in the art because it is common in the art to target tumors/cancers with anticancer targeting ligands.

CLAIM OBJECTIONS

6. Claims 71, 72, 74-78, 81, and 82 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Note: The claims are distinguished over the prior art of record because the prior art neither anticipates nor renders obvious the limitations in the dependent claims in combination with their respective intervening claims.

7. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to D. L. Jones whose telephone number is (571) 272-0617. The examiner can normally be reached on Mon.-Fri., 6:45 a.m. - 3:15 p.m..

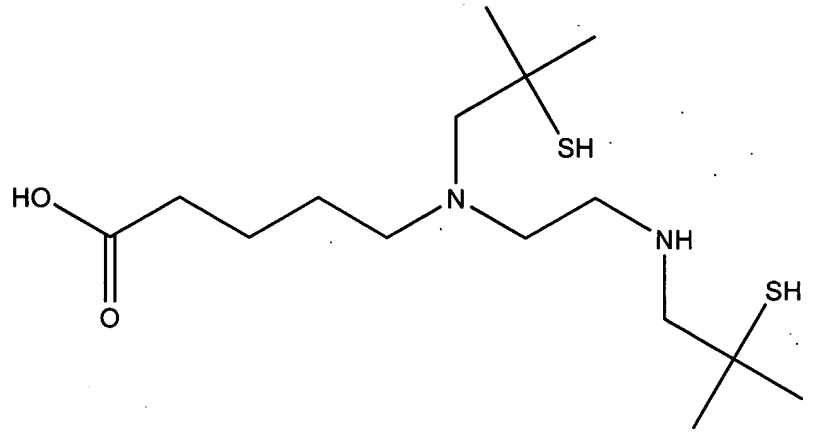
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on (571) 272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

D. L. Jones
Primary Examiner
Art Unit 1618

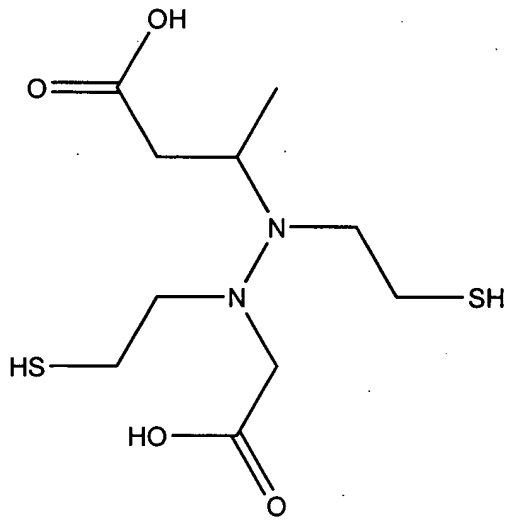
September 29, 2006

Structure from US Patent No. 5,620,675
(Col 12, lines 29-30)



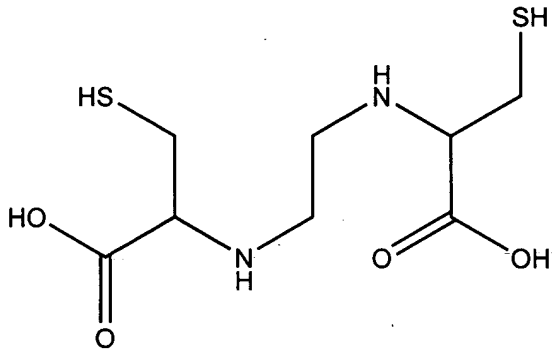
N6,N9-bis(2-mercapto-2-methylpropyl)-6,9-diazanonanoic acid

Structure from US Patent No. 4,925,650 (column 4, lines 43-44)



n,n'-[bis(2-mercaptoethyl)]-n,n',-ethylenediamindiacetic acid

Structure from US Patent No. 4,925,650 (column 4, line 39)



N,N'-bis(1-carboxy-2-mercaptoethyl)ethylene diamine